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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/715,927 | 11/17/2000 | Leonard I. Zon | 1242.1035-002 | 6132 |

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| EXAMINER | |
|---|---|
| WEGERT, SANDRA L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | 28 |

DATE MAILED: 11/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/715,927 | ZON ET AL. | |
| | Examiner | Art Unit | |
| | Sandra Wegert | 1647 | |

*-- The MAILING DATE of this communication appears on the cov r she t with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *7/28/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-52,54-62,65,67-72 and 134-139* is/are pending in the application.

4a) Of the above claim(s) *1-45* is/are withdrawn from consideration.

5)☒ Claim(s) *46 and 72* is/are allowed.

6)☐ Claim(s) *47-52,54-62,65,67-71 and 134-139* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-52,54-62,65,67-72 and 134-139* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

***Status of Application, Amendments, and/or Claims***

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

The Information Disclosure Statement and Amendment, received 30 July 2003, has been entered into the record. Applicants cancelled Claims 53, 63, 64, 66 and 73-133 and added Claims 134-139. Claims 1-45 were withdrawn by the examiner in Paper 12 (31 July 2002).

Claims 46-52, 54-62, 65, 67-72 and 134-139 are being examined in the instant Application, as pertaining to SEQ ID NO: 5 and 7.

***Withdrawn Objections/Rejections***

***35 USC § 102, Prior Art***

The rejection of Claims 55, 58, 64 and 68, under 35 USC 102(b), as set forth at pages 10-11 in the previous Office Action (31 July 2003), is *withdrawn.* Claims 55, 58, 64 and 68 read on portions of the transporter polypeptide that have "iron transport activity," which is unlike the polypeptide of the Fujiwara, et al (1995) reference.

## ***Objections/Rejections***

### *35 USC § 112, first paragraph-Scope of Enablement*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 47-52, 54-62, 65, 67-71 and 134-139 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleic acids of SEQ ID NO: 5 and 7, encoding the Ferroportin1 transporter of SEQ ID NO: 6, does not reasonably provide enablement for: nucleic acids with 80% sequence identity to SEQ ID NO: 5 or 7; nucleic acid *fragments* or *portions*, or encoding *portions* or *fragments* of SEQ ID NO: 6; or *allelic variants* of SEQ ID NO: 6, without specifying the exact sequence variation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to cDNA and genomic DNA encoding a human iron transporter polypeptide. The specification discloses human, mouse and Zebrafish iron transporters and uses the Zebrafish transporter to measure iron flux across Xenopus oocytes transfected with the polynucleotide(s) encoding the transporter. The specification also discloses methods for recombinantly expressing the disclosed transporter polypeptides. The human and mouse polypeptides have approximately 82 and 89% similarity to the Zebrafish iron transporter, respectively. Furthermore, the Applicant's post filing-date reference demonstrates that the human Ferroportin transporter functions similarly to the Zebrafish iron transporter (Montosi, et

al, 2001, J. Clin. Invest., 108(4): 619-623). However, the scope of the patent protection sought by the Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons:

The specification discloses an enabled utility for the polypeptide encoded by the DNA of SEQ ID NO: 1, as to be used to transport iron across the plasma membrane of cells expressing or transfected with the polynucleotide. Since the transporter of SEQ ID NO: 1 is an iron *exporter* (see p. 59 and Fig. 3) it must be used in concert with an iron *importer* to facilitate measurement of iron flux across transfected cells. Applicants have demonstrated, using transfected Xenopus oocytes, that the polypeptide encoded by SEQ ID NO: 1 (SEQ ID NO: 2) is a transmembrane transporter. Furthermore, by performing the iron flux experiments in the presence and absence of an iron chelator, they have demonstrated that the transporter binds and translocates *iron* specifically. By further transfecting the cells with a known iron transporter that translocates iron *into* cells, they have shown that the Zebrafish ferroportin transports iron *out* of a cell.

However, the specification is not enabling for various forms of the polypeptide encoded by SEQ ID NO: 5 and 7, wherein the DNA sequence is *at least 80%* identical to the nucleic acid sequence(s) encoding SEQ ID NO: 6, as recited in claims 47, 54, 57, 60, 62, 67, 70 and 71. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are directed to a polynucleotide encoding a ferroportin transporter polypeptide. The specification discloses mouse, human and Zebrafish transporters

The specification discloses the human transporter encoded by the DNA of SEQ ID NO: 5 and 7. However, there is no discussion, or working examples disclosed in the instant case, as to what amino acids are necessary to impart or maintain the functional characteristics of the claimed polynucleotide(s). The instant case claims altering as much as 20% of the polynucleotide(s) encoding the polypeptide of SEQ ID NO: 6. However, as discussed in the previous Office Action (pages 6-9, 31 July 2002) the art shows that transporter families have members with high structural similarities but disparate functions. For example, Bisson, *et al* (1993, Crit Rev Biochem Mol Biol, 28:259) studied yeast transporter knockout phenotypes, and found little correlation between homology and the substrate transported. They determined that yeast transporters *Gal2* and *Hxt4* displayed 83.7% homology, but *Gal2* appears to transport Galactose, while *Hxt4* appears to transport Glucose (based on knockout phenotype- compare Table 1 and Table 2A). Similarly, Liang et al found that several single amino acid substitutions in yeast glucose transporters can also change substrate specificity (Liang, H., et al (1998) Mol. Cell. Biol. 18(2): 926). These studies demonstrate that it is not predictable which amino acids are necessary to maintain the functional characteristics of a protein.

For similar reasons, the specification is not enabling for various *regions, fragments or portions* of the polypeptide encoded by SEQ ID NO: 5 and 7, as in claims 48, 49, 50, 51, 52, 55, 56, 58, 59, 61, 63, 65, 68, 69, 135, 136, 138 and 139. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Claims 48, 49, 50, 51, 52, 55, 56, 58, 59, 61, 63, 65, 68, 69, 135, 136, 138 and 139 read on defined and undefined fragments of the polynucleotide(s) encoding SEQ ID NO: 6. However, the specific activities of the proteins

encoded by the claimed nucleotide fragments are not disclosed. Nor are there disclosed assays to test for these activities. There is no discussion or working examples disclosed in the instant case as to what amino acids are necessary to maintain the functional characteristics of the polypeptide fragments encoded by the claimed polynucleotides.

Furthermore, the specification does not reasonably provide enablement for use of the polypeptide or polynucleotide *allelic variants,* as recited in claims 51, 134 and 137. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Applicants have not identified all allelic variants of the Ferroportin1 protein encompassed by the claims, nor of the polynucleotide(s) encoding SEQ ID NO: 6. Claims 51, 134 and 137 encompass numerous undefined variants of SEQ ID NO: 5 and 7, without precise recitations of function that can be applied to allelic variants, nor by reciting the expected amino acid substitutions found in a claimed allelic variant. Furthermore, as discussed above, it is not predictable as to which possible variants are tolerated while still maintaining the functional characteristics of a protein. Applicants have submitted evidence from their laboratory indicating that the polynucleotide encoding SEQ ID NO: 6 does have a single known allelic variant, characterized by an *A77D* substitution (alanine to aspartate at residue 77) and responsible for a dominant hemochromatosis (Montosi, et al, 2001, J. Clin. Invest., 108(4): 619-623). However, claims 51, 134 and 137 read on many unidentified allelic variants, rather than the documented *A77D* substitution.

Due to the large quantity of experimentation required to: determine how to use all variants of SEQ ID NO: 5 and 7; the lack of direction or guidance in the specification regarding

same - e.g., the lack of guidance regarding activity of the fragments of the polynucleotides; the lack of guidance regarding allelic variants of SEQ ID NO: 5; the lack of guidance as to polynucleotides that are at least 80% identical; the lack of working examples to all variants of SEQ ID NO: 5 and 7; the state of the art showing the unpredictability of function based on structural similarity of transporter polypeptides; and the breadth of the claims which embrace innumerable variants of SEQ ID NO: 5 and 7-- undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Conclusion:

Claims 46 and 72 are allowable.

Claims 47-52, 54-62, 65, 67-71 and 134-139 are rejected for the reasons cited above.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. (Note: after 21 January 2004, the Examiner's phone number will be (571) 272-0895). The examiner can normally be reached Monday - Friday from 9:30 AM to 6:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623. Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

SLW

11/5/03